In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS
No. 18-554V
Filed: November 10, 2022
PUBLISHED

SCOTT ROBERTSON, Petitioner, v. SECRETARY OF HEALTH AND HUMAN SERVICES, Respondent.	Special Master Horner Optic neuritis ("ON"); nonarteritic anterior ischemic optic neuropathy ("NAION"); Influenza ("flu") vaccine

Ronald Homer, Conway, Homer, P.C., Boston, MA, for petitioner.
Voris Johnson, U.S. Department of Justice, Washington, DC, for respondent.

DECISION[1]

On April 17, 2018, petitioner filed a petition under the National Childhood Vaccine Injury Act, 42 U.S.C. § 300aa-10-34 (2012),[2] alleging that the influenza ("flu") vaccine he received on October 28, 2016, caused him to suffer relapsing optic neuropathy and/or neuritis. (ECF No. 1, p. 1.) Subsequently, the parties' experts agreed that the best diagnosis for petitioner's condition is nonarteritic anterior ischemic optic neuropathy ("NAION"). (Ex. 30, p. 1; Ex. B, p. 5.) On August 13, 2021, petitioner filed his motion for a ruling on the record alleging that the flu vaccine caused-in-fact his NAION. (ECF No. 65, pp. 1 n.2, 27-29.) For the reasons set forth below, I conclude that that petitioner is not entitled to compensation.

[1] Because this decision contains a reasoned explanation for the special master's action in this case, it will be posted on the United States Court of Federal Claims' website in accordance with the E-Government Act of 2002. *See* 44 U.S.C. § 3501 note (2012) (Federal Management and Promotion of Electronic Government Services). **This means the decision will be available to anyone with access to the Internet.** In accordance with Vaccine Rule 18(b), petitioner has 14 days to identify and move to redact medical or other information the disclosure of which would constitute an unwarranted invasion of privacy. If the special master, upon review, agrees that the identified material fits within this definition, it will be redacted from public access.

[2] Within this decision, all citations to § 300aa will be the relevant sections of the Vaccine Act at 42 U.S.C. § 300aa-10-34.

I. Applicable Statutory Scheme

Under the National Vaccine Injury Compensation Program, compensation awards are made to individuals who have suffered injuries after receiving vaccines. In general, to gain an award, a petitioner must make a number of factual demonstrations, including showing that an individual received a vaccination covered by the statute; received it in the United States; suffered a serious, long-standing injury; and has received no previous award or settlement on account of the injury. Finally – and the key question in most cases under the Program – the petitioner must also establish a *causal link* between the vaccination and the injury. In some cases, the petitioner may simply demonstrate the occurrence of what has been called a "Table Injury." That is, it may be shown that the vaccine recipient suffered an injury of the type enumerated in the "Vaccine Injury Table," corresponding to the vaccination in question, within an applicable time period following the vaccination also specified in the Table. If so, the Table Injury is presumed to have been caused by the vaccination, and the petitioner is automatically entitled to compensation, unless it is affirmatively shown that the injury was caused by some factor other than the vaccination. § 300aa-13(a)(1)(A); § 300 aa-11(c)(1)(C)(i); § 300aa-14(a); § 300aa-13(a)(1)(B).

In many cases, however, the vaccine recipient may have suffered an injury *not* of the type covered in the Vaccine Injury Table. In such instances, an alternative means exists to demonstrate entitlement to a Program award. That is, the petitioner may gain an award by showing that the recipient's injury was "caused-in-fact" by the vaccination in question. § 300aa-13(a)(1)(B); § 300aa-11(c)(1)(C)(ii). In such a situation, of course, the presumptions available under the Vaccine Injury Table are inoperative. The burden is on the petitioner to introduce evidence demonstrating that the vaccination actually caused the injury in question. *Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278 (Fed. Cir. 2005); *Hines v. Sec'y of Health & Human Servs.*, 940 F.2d 1518, 1525 (Fed. Cir. 1991).

The showing of "causation-in-fact" must satisfy the "preponderance of the evidence" standard, the same standard ordinarily used in tort litigation. § 300aa-13(a)(1)(A); *see also Althen*, 418 F.3d at 1279; *Hines*, 940 F.2d at 1525. Under that standard, the petitioner must show that it is "more probable than not" that the vaccination was the cause of the injury. *Althen*, 418 F.3d at 1279. The petitioner need not show that the vaccination was the sole cause but must demonstrate that the vaccination was at least a "substantial factor" in causing the condition, and was a "but for" cause. *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352 (Fed. Cir. 1999). Thus, the petitioner must supply "proof of a logical sequence of cause and effect showing that the vaccination was the reason for the injury[,]" with the logical sequence being supported by "reputable medical or scientific explanation, *i.e.*, evidence in the form of scientific studies or expert medical testimony." *Althen*, 418 F.3d at 1278; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). A petitioner may not receive a Vaccine Program award based solely on his or her assertions; rather, the petition must be supported by either medical records or by the opinion of a competent physician. § 300aa-13(a)(1).

In what has become the predominant framing of this burden of proof, the *Althen* court described the "causation-in-fact" standard, as follows:

> Concisely stated, Althen's burden is to show by preponderant evidence that the vaccination brought about her injury by providing: (1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of proximate temporal relationship between vaccination and injury. If Althen satisfies this burden, she is "entitled to recover unless the [government] shows, also by a preponderance of the evidence, that the injury was in fact caused by factors unrelated to the vaccine."

Althen, 418 F.3d at 1278 (citations omitted). The *Althen* court noted that a petitioner need not necessarily supply evidence from medical literature supporting petitioner's causation contention, so long as the petitioner supplies the medical opinion of an expert. *Id*. at 1279-80. The court also indicated that, in finding causation, a Program factfinder may rely upon "circumstantial evidence," which the court found to be consistent with the "system created by Congress, in which close calls regarding causation are resolved in favor of injured claimants." *Id*. at 1280.

In this case, petitioner has alleged that the flu vaccine caused him to suffer nonarteritic anterior ischemic optic neuropathy ("NAION"). (ECF No. 65, pp. 1 n.2, 27-29.) Since NAION is not listed on the Vaccine Injury Table relative to the flu vaccine, petitioner must satisfy the above-described *Althen* test for establishing causation-in-fact.

II. Procedural History

On April 17, 2018, petitioner filed a petition alleging that he received a flu vaccine on October 28, 2016, that caused relapsing optic neuropathy and/or neuritis. (ECF No. 1, p. 1.) This case was originally assigned to Special Master Sanders. (ECF No. 4.) On April 20, 2018, petitioner filed his affidavit and medical records. (ECF Nos. 8-10.) From May 21, 2018, through April 22, 2019, petitioner subsequently filed additional medical records. (ECF Nos. 13, 19, 21, 25.) On May 16, 2019, respondent filed his Rule 4(c) report, arguing that the evidence presented did not meet petitioner's burden and recommending against compensation. (ECF No. 28.) Respondent further argued that petitioner's diagnosis appeared to be CRION, a "separate clinical entity from monophasic ON and its key clinical features include relapsing inflammatory ON and steroid dependency." (*Id.* at 7.)

This case was reassigned to my docket on August 28, 2019. (ECF No. 34.) On October 9, 2019, petitioner filed additional medical records. (ECF No. 37.) On November 18, 2019, petitioner filed an expert report from Thomas Hedges III, M.D. (neuro-ophthalmologist). (ECF No. 40.) On March 31, 2020, respondent filed an expert report from Michael Wilson, M.D., MAS (neuroimmunologist). (ECF No. 44.)

Subsequently both parties filed supplemental expert reports on April 29 and June 30, 2020. (ECF No. 45 (Dr. Hedges); ECF No. 48 (Dr. Wilson).).

A Rule 5 conference was held on September 18, 2020. (ECF No. 50.) In the subsequent Rule 5 Order, I noted that diagnosis was an unresolved issued in this case. (*Id.*) In his petition, petitioner alleged that he suffered either optic neuritis or neuropathy; and respondent disputed optic neuritis as a diagnosis but suggested a type of neuropathy. (*Id.*) Petitioner's expert Dr. Hedges opined that petitioner's diagnosis is nonarteritic ischemic optic neuropathy. (*Id.*) Respondent's expert Dr. Wilson agreed with the assessment of NAION though he did not dismiss the possible diagnosis of optic neuritis. (*Id.*) With regard to causation, I observed that Dr. Hedges cited four case reports showing that NAION can occur post-influenza vaccination (Ex. 24, p. 2), though I cautioned that standing alone these case reports are not highly persuasive. (ECF No. 50.)

On January 19, 2021, petitioner filed an expert report from Omid Akbari, Ph.D. (allergy and immunology). (ECF Nos. 53-57.) Respondent filed a responsive expert report from Dr. Wilson on March 23, 2021. (ECF No. 60.) On June 14, 2021, the parties filed a joint status report proposing a ruling on the written record. (ECF No. 64.) On August 13, 2021, petitioner filed his motion for a ruling on the record. (ECF No. 65.) On October 13, 2021, respondent filed his responsive brief. (ECF No. 66.) On November 10, 2021, petitioner filed his reply. (ECF No. 68.)

I have determined that the parties have had a full and fair opportunity to present their cases and that it is appropriate to resolve this issue without a hearing. *See* Vaccine Rule 8(d); Vaccine Rule 3(b)(2); *Kreizenbeck v. Sec'y of Health & Human Servs*., 945 F.3d 1362, 1366 (Fed. Cir. 2020) (noting that "special masters must determine that the record is comprehensive and fully developed before ruling on the record."). Accordingly, this matter is now ripe for resolution.

III. Factual History

a. As reflected in the medical records

Prior to vaccination, petitioner's history was significant for a motor vehicle accident in March 2014 with cervical and lumbar pain. (Exs. 5, 12, 15.) He also had a history of tobacco use, hypertension, and hyperlipidemia. (*See*, *e.g.*, Ex. 5, pp. 1-2 (4/18/2017 record listing hypertension and hyperlipidemia as active problems, and noting "[c]urrent everyday [sic] smoker"); *id*. at 13 (7/16/2014 record noting "tobacco use" under the social history section); Ex. 7, p. 2 (12/22/2016 record noting that petitioner "[c]hews tobacco").) Petitioner also suffers from obstructive sleep apnea. (Ex. 2, p. 5.)

Petitioner received a Fluvirin vaccine on October 28, 2016. (Ex. 1, p. 1.) On December 5, 2016, petitioner presented to Jennifer Roman, O.D., complaining of blurry vision in his left eye. (Ex. 13, p. 11.) He reported a sudden onset on Tuesday

(November 29), which had slowly worsened over the last couple of days. (*Id.*) Petitioner indicated that he recently had a cold. (*Id*. at 11; *see also* Ex. 3, pp. 4-8 (petitioner reporting that he had a cold over Thanksgiving).) On examination, the optometrist observed left optic disc swelling. (Ex. 13, pp. 11-16; Ex. 3, p. 3.) Dr. Roman referred petitioner to the emergency room for suspected NAION. (Ex. 13, p. 16.)

That same day, December 5, 2016, petitioner presented to the Emergency Department ("ED") at UF Health Shands. (Ex. 3, p. 3.) He reported noticing floaters / spots in his left field of vision approximately three-to-four days earlier, which had enveloped his whole eye. (*Id.*) Petitioner also reported eye pressure but denied eye pain. (*Id*. at 4-6.) A review of systems was positive for nasal congestion and discharge. (*Id*. at 4.) His differential diagnoses included papilledema, optic neuropathy, anterior ischemic optic neuropathy, and papillophlebitis. (*Id*. at 5.) An ophthalmologist was consulted and ordered a brain MRI, which confirmed the presence of left-sided palpable edema without associated enhancement and changes of chronic ischemic white matter demyelination in the brain as seen in the setting of chronic small vessel disease. (*Id.* at 6, 52-53.) There was no evidence of an intracranial mass lesion, infectious / inflammatory process, or MR findings of intracranial hypertension. (*Id*. at 6.) The ophthalmologist diagnosed petitioner with optic nerve swelling and optic atrophy of the left eye of unknown etiology, and recommended Brimonidine eye drops. (*Id*.) Petitioner was discharged the following day to follow up with an ophthalmologist. (*Id*. at 6, 14.)

On December 9, 2016, petitioner was evaluated by ophthalmologist Stephen Potter, M.D., at the University of Florida ("UF") Eye Center for painless vision loss and optic disc edema in the left eye. (Ex. 8, p. 1.) He also developed atrophy in his left eye. (*Id*. at 10.) The ophthalmologist indicated that petitioner's differential diagnosis was "most likely post-vaccination optic neuritis given flu-shot 1 month prior to presentation vs post-infectious optic neuritis (less likely given negative labs; baronella [sic] pending) vs autoimmune optic neuritis (MS-spectrum)." (*Id*. at 2; Ex. 4, p. 43.) He recommended admission to the hospital for treatment with intravenous ("IV") steroids. (Ex. 8, p. 2.) Petitioner was subsequently admitted to the hospital for three days of treatment with IV steroids and then discharged with an oral steroid taper. (Ex. 4, pp. 39-44; Ex. 19, pp. 4-5.)

On January 5, 2017, petitioner presented to neuro-ophthalmologist Hazem Samy, M.D., at the UF Eye Center. (Ex. 8, pp. 4-5.) Dr. Samy diagnosed petitioner with left eye papillitis "[p]ost-vaccination vs post-infectious vs autoimmune optic neuritis (MS-spectrum . . . Received flu vaccine 1 month prior to presentation." (*Id.*) Petitioner reported improved visual acuity and visual field as well as resolved edema. (*Id.*) Dr. Samy ordered petitioner to continue taking Brimonidine and "[a]void flu vaccination in future." (*Id.*)

On January 27, 2017, petitioner returned to Dr. Samy with new onset of mild swelling / edema of the optic nerve with flame hemorrhage in his right eye. (Ex. 8, pp. 9-15.) Dr. Samy started petitioner on treatment with oral prednisone. (*Id.* at 11.)

Petitioner returned to Dr. Samy emergently almost a week later, on February 2, 2017, complaining of worsening blurry vision in his right eye. (*Id*. at 15.) Dr. Samy suspected possible sequential NAION of the right eye. (*Id*. at 15-16.) Petitioner had mild inferior optic nerve edema, which was stable since his previous visit. (*Id*.) Dr. Samy recommended continuing treatment with prednisone. (*Id*. at 16.) In follow-up two weeks later, petitioner's vision was stable. (*Id*. at 17.)

Petitioner returned to Dr. Samy's office on March 12, 2017, complaining of worsening visual disturbances in his right eye with decreasing prednisone dosage. (Ex. 8, p. 22.) The doctor recommended that petitioner go to the hospital to receive another round of IV steroids. (*Id*. at 25; Ex. 3, pp. 82-83.) The ER sent petitioner to the infusion center for treatment to avoid having to be admitted to the hospital. (*Id*. at 87.) Petitioner subsequently received two days of IV steroids for right ischemic optic neuropathy. (Ex. 10, pp. 1-50.)

Petitioner followed up with Dr. Samy on March 16, 2017, complaining that his right eye seemed worse. (Ex. 8, p. 26.) Dr. Samy's impression based on petitioner's presentation and clinical course was that he had chronic relapsing AION.[3] (*Id*. at 30.) Petitioner continued to follow up with Dr. Samy for CRON in April, May, and July 2017. (Ex. 5, pp. 1-6; Ex. 8, pp. 32-37; Ex. 19, pp. 1-5.) A skin punch biopsy collected on April 14, 2017, showed no evidence of vasculitis or vasculopathy. (Ex. 8, p. 44.) At a May 19, 2017 visit, Dr. Samy noted that petitioner had slight improvement in his visual field defects and stable visual acuity. (*Id*. at 38.)

On April 4, 2017, petitioner established care with a new primary care physician, Brian Pecoraro, D.O., at Ocala Family Wellness Center. (Ex. 5, p. 7.) Dr. Pecoraro noted in petitioner's active problems optic neuritis—for which he was being monitored by ophthalmology and treated with steroids. (*See*, *e.g*., Ex. 5, pp. 1-5.)

On July 7, 2017, petitioner complained to Dr. Samy that his vision had been off for the past four days after tapering his prednisone. (Ex. 19, pp. 4-5.) Dr. Samy recommended starting CellCept, an immune-modulating agent. (*Id*.) However, because it would take about three months for CellCept to be effective, Dr. Samy recommended another round of IV steroids followed by increasing petitioner's prednisone in the interim. (*Id*. at 5.) Consequently, petitioner received three days of IV steroids at the infusion center from July 12 through 14, 2017. (*Id*. at 6; Ex. 10, pp. 50-110.)

In follow-up on July 21, 2017, petitioner indicated that his vision was off in the previous visit. (Ex. 19, pp. 11-12.) Petitioner underwent subsequent C-spine MRI to rule out neuromyelitis optica. (Ex. 22, pp. 1-2.) The impression was "[n]o evidence of abnormal T2 signal changes or abnormal contrast enhancement of the cervical or thoracic spinal cord which could suggest inflammation/demyelination." (*Id.* at 2.) There

[3] Dr. Samy maintained the diagnosis of CRON (chronic relapsing optic neuropathy) throughout subsequent visits, noting sequential NAION as a previous impression. (*See*, *e.g*., Ex. 5, pp. 1-6; Ex. 8, pp. 32-37; Ex. 19, pp. 1-35; Ex. 21, pp. 1-3.)

was no significant disc disease or canal narrowing in the cervical or thoracic spine. (*Id.*) Thereafter, petitioner followed up with Dr. Samy on August 11, September 22, and December 14, 2017; and on February 23, May 25, and November 12, 2018, for CRON. (Ex. 19, pp. 13-39; Ex. 21, pp. 1-3.) During that time, petitioner experienced some improvement in his visual acuity and visual fields on prednisone and CellCept, and there was no recurrence of inflammation in the optic nerves. (*Id.*) Petitioner discontinued prednisone in February 2018 without a subsequent change in his vision. (Ex. 19, pp. 34-35.) In his November 12, 2018, visit Dr. Samy remarked that petitioner developed "optic neuropathy [in] early 2017 which was post vaccination but in a pattern suggestive of possible ischemia in disc without cup followed by a few months later with the other eye." (Ex. 21, p. 3.) "The clinical course of the optic neuropathy showed recurrences after tapering of the oral steroid which made the diagnosis CRION (chronic relapsing inflammatory optic neuropathy)." (*Id.*) Dr. Samy explained to petitioner he would need to taper off the CellCept and continue regular blood testing. (*Id.* at 4.)

b. Petitioner's affidavit

On October 28, 2016, petitioner received a flu vaccine at his local Walgreens. (Ex. 16, p. 1.) Several weeks later, shortly after Thanksgiving, petitioner describes losing vision in his left eye, "[i]t started as a hazy halo around the outside of my left eye, which progressively closed in and led to a complete loss of vision in my left eye when I woke up on December 5, 2016." (*Id.* at 1-2.) That day petitioner presented to an optometrist who sent him to the emergency room at Shands Hospital in Gainesville, Florida. (*Id.* at 2.) He was discharged on December 6, 2016, and told to follow up with an ophthalmologist. (*Id.*)

Petitioner returned to work soon after discharge. (Ex. 16, p. 2.) Petitioner avers that he was concerned that his employer would feel that he was unable to work due to his vision loss. (*Id.*) While on the job petitioner suffered a right thumb injury while operating a spring-loaded jack. (*Id.*) In January 2017, petitioner avers that he established care with ophthalmologist Dr. Hazem Samy. (*Id.* at 3.) Despite treatment petitioner asserts that he still had significant deficits in his vision in his left eye. (*Id.*)

Subsequently petitioner began to experience vision issues in his right eye in March 2017. (Ex. 16, p. 3.) He avers that he was "more aware of what was occurring with [his] right eye," so he immediately went to Dr. Samy's office, where he saw Dr. Andres Gonzalez, who sent him directly to Shands Hospital to receive three days of IV steroid treatments. (*Id.*) Petitioner avers that following his onset of optic neuritis, his vision loss has been permanent. (*Id.*) He continued taking steroids to prevent further episodes, which caused additional health issues. (*Id.*) Petitioner describes taking Metformin, arnica (due to bruising that developed after taking steroids), vitamin B12 and CoQ10 supplements, and using an APAP machine. (*Id.*)

Petitioner avers that his condition caused him to miss three to four weeks of work, and that he can no longer perform mechanic or welding work because of his difficulties with depth perception. (Ex. 16, pp. 3-4.) As a result, petitioner avers that he

"need[s] to be much more cautious at work and [his] end product is not as good as it was prior to [his] vision loss." (*Id.*) He asserts that he is unable to do his job to the best of his ability and is concerned about future employment. (*Id.*)

Petitioner describes difficulty watching his daughter's softball games and award ceremonies. (Ex. 16, p. 4.) His condition also impacts his ability to drive, especially at night. (*Id.* at 5.) He avers that he faces financial instability due to the medical bills he incurred during treatment. (*Id.*) Petitioner continues follow-up treatment with Dr. Samy every sixty to ninety days. (*Id.*) He avers that his vision has stabilized but has not improved. (*Id.* at 6.) Petitioner describes a small area of tunnel vision in the bottom right-hand corner of his left eye, a hazy halo around the outside of the eye, and a blind spot in the lower right-hand corner of his right eye. (*Id.*)

IV. Summary of Expert Opinions

a. Petitioner's Experts

i. Thomas R. Hedges, III, M.D.

Dr. Hedges received his medical degree from Tufts University. (Ex. 25.) He completed his residency in ophthalmology at Massachusetts Eye and Ear Infirmary at Harvard Medical School. (*Id.*) Dr. Hedges completed an ophthalmic pathology fellowship at that the Massachusetts Eye and Ear Infirmary at Harvard Medical School. (*Id.*) He subsequently completed a fellowship in neuro-ophthalmology at the University of California, San Francisco. (*Id.*) Dr. Hedges is board certified in ophthalmology. (*Id.*) He has served as an ophthalmologist at Tufts Medical Center since 1991. (*Id.*) He currently serves as a professor of ophthalmology and neurology at Tufts University. (*Id.*) His research interests include qualitative and quantitative evaluation of the retinal nerve fiber layer using photographic methods, computerized image enhancement, and Optical Coherence Tomography; Color Doppler imaging of orbital and extracranial blood vessels in vascular diseases affecting the eye; multifocal electroretinography and visual evoked potential recording. (*Id.*) He has co-authored several works on optic and peripheral neuropathy. (*Id.*)

Dr. Hedges opines that petitioner's correct diagnosis is NAION. (Ex. 24, p. 1.) According to Dr. Hedges, anterior ischemic optic neuropathy is relatively common, but the exact pathogenesis is unknown. (*Id.* at 2.) It appears to be multifactorial, with various associations, but no one direct cause has been identified. (*Id.*) Dr. Hedges observes that petitioner has some of the associated risk factors, including hypertension and sleep apnea, but he stresses that "these are associations, not direct causative factors." (*Id.*) Dr. Hedges opines that these risk factors combined with a physiologic response to vaccination "pushed beyond normal function and past regulatory mechanisms, more likely than not, resulted in injury to [petitioner's] optic nerves." (*Id.*) He asserts that the most plausible mechanism is that of immune complex mediated vasculopathy/vasculitis, leading to inflammation and resultant ocular nerve injury. (*Id.*) This is a form of type III hypersensitivity whereby proteins contained in the vaccine

stimulate an antibody reaction causing formation of antigen-antibody complexes, which can block small blood vessels or attach to the walls of small blood vessels stimulating inflammation and then blockage of the vessels leading to damage, in this case, to the optic nerve. (*Id.*)

In support of his theory, Dr. Hedges observes that post-vaccination optic neuritis is well-documented in the medical literature and is believed to be similar to other instances of damage to other cranial nerves following vaccination, especially with regard to the seventh nerve (Bell's) palsy following vaccination. (Ex. 24, p. 2 (citing Janaki Patel et al., *Development of Optic Neuritis After Vaccination, a CDC/FDA Vaccine Adverse Event Reporting System (VAERS) Study, 1990-2017*, 90 NEUROLOGY 1 (2018) (Ex. 26)).) Dr. Hedges cites four case reports of anterior ischemic neuropathy following vaccination. (*Id.*) In 1998, Kawasaki et al. reported two cases of anterior ischemic optic neuropathy following influenza vaccination. (*Id.* (citing Aki Kawasaki et al., *Bilateral Anterior Ischemic Optic Neuropathy Following Influenza Vaccination,* 18 J. NEURO-OPHTHALMOLOGY 56 (1998) (Ex. 27)).) The authors postulated that an immune complex-mediated vasculopathy caused the optic nerve damage. (*Id.*) Next, Dr. Hedges cites Ray and Dreizin, who reported a case of a 61-year-old man with bilateral optic neuropathy "similar to [petitioner] who had some response to steroid treatment." (*Id.* (citing Cheryl Ray & Ivy Dreizin, *Bilateral Optic Neuropathy Associated with Influenza Vaccination,* 16 J. NEURO-OPHTHALMOLOGY 182 (1996) (Ex. 28)).) Most recently, Manasseh et al. reported another case of bilateral sequential NAION following repeat influenza vaccination. (*Id.* (citing Gemma Manasseh et al., *Bilateral Sequential Non-Arteritic Anterior Ischaemic Optic Neuropathy Following Repeat Influenza Vaccination,* 5 CASE REP. OPHTHALMOLOGY 267 (2014) (Ex. 29)).) Like Kawasaki et al., the authors opined that immune complex vasculitis was a more likely mechanism than demyelination damaging the optic nerve.

Regarding timing, Dr. Hedges opines that petitioner experienced onset of symptoms approximately 4.5 weeks post vaccination. (Ex. 24, p. 2.) He opines that this is an appropriate timeframe for symptom development because immune-mediated disorders typically develop within 6 to 8 weeks following a triggering event. (*Id.*) Moreover, Dr. Hedges represents that this is consistent with the timing of symptom onset in the case reports. (*Id.*) On average those patients experienced onset of NAION within one to four weeks post-flu vaccination. (*Id.*)

In his supplemental report, Dr. Hedges opines that skin biopsies in patients with immune hypersensitivity reactions are "frequently normal, especially when performed months later." (Ex. 30, p. 1.) Petitioner's skin biopsy was performed in April 2017, over six months post-vaccination. (*Id.*) Respondent's expert Dr. Wilson argues that a temporally proximate viral illness may have equally served as an infectious trigger for petitioner's injury. (Ex. B.) In response, Dr. Hedges opines that any potential illness is ill-defined, and no viral or bacterial infection was ever identified. (Ex. 30, p. 1.) Furthermore, he stresses that upper respiratory infections are common, frequently coincidental and generally not considered to be associated with or causal of ON or NAION. (*Id.* at 1-2.)

ii. Omid Akbari, Ph.D.

Dr. Akbari received his Master of Science degree from the University College of London. (Ex. 32.) He received his Ph.D. in cellular and molecular immunology from the National Institute for Medical Research in London. (*Id.*) Dr. Akbari completed his postdoctoral fellowship at Stanford University. (*Id.*) He currently serves as a professor of Allergy and Immunology and professor of Medicine at Keck School of Medicine, University of Southern California. (Ex. 31.) Prior to that Dr. Akbari was an assistant professor at Harvard Medical School and held an appointment as senior scientist at Stanford University. (*Id.*) Dr. Akbari's research is focused on the role of immune tolerance and how immune cells induce autoimmune and allergic diseases. (*Id.*) He has served on several NIH study sections, including special emphasis panel related to research in vaccine, infectious diseases, and immunology. (*Id.*)

Regarding petitioner's diagnosis, Dr. Akbari observed that "[t]he possibility of [optic neuritis] was not ruled out as some patients with ON are steroid refractory and do not exhibit demyelination in regular MRI scan." (Ex. 31, p. 3.) He acknowledges that Dr. Hedges and Dr. Wilson have opined that petitioner may have atypical optic neuritis, though it is more likely that he suffers from NAION. (*Id.*) Still, in his expert report Dr. Akbari discusses how the flu vaccine can cause optic neuritis and/or vasculitis, leading to ischemic complications and optic nerve injury. (*Id.*)

First Dr. Akbari proposes a theory of molecular mimicry, "which support[s] the notion and describe[s] how [the] influenza vaccine can induce immune responses, which are often associated with inflammation, vasculitis[,] and optic nerve injury." (Ex. 31, p. 6-8.) He cites two studies involving multiple sclerosis, neuromyelitis and demyelinating disease. (*Id.* at 6.) Markovic-Plese et al. proposed cross-reactivity of a CD4+ T-cell clone specific for the immunodominant influenza virus hemagglutinin peptide (sequence YVKQSTLKL) derived from a patient with neuromyelitis and demyelinating disease, including MS. (Silva Markovic-Plese et al., *High Level of Cross-Reactivity in Influenza Virus Hemagglutinin-Specific CD4+ T Cell Response: Implications for the Initiation of Autoimmune Response in Multiple Sclerosis*, 169 J. NEUROIMMUNOLOGY 31 (2005) (Ex. 50)).) In another study by Harvard group Wucherpfennig et al., a panel of 129 peptides that matched the molecular mimicry motif was tested on seven specific T cell clones from patients with neuromyelitis and demyelinating disease. (Kai Wucherpfennig et al., *Recognition of the Immunodominant Myelin Basic Protein Peptide by Autoantibodies and HLA-DR2-Restricted T Cell Clones from Multiple Sclerosis Patients,* 100 J. CLIN. INVEST. 1114 (1997) (Ex. 54)).) Seven viral and one bacterial peptide efficiently activated three of these clones. (*Id.*) From these studies Dr. Akbari proposes that the influenza vaccine petitioner received "contains a protein that cross-reacts with myelin based antigens in humans who had demyelinating disease." (Ex. 31, p. 6.) Dr. Akbari draws support for this theory from studies showing that self-reactive T cells were also shown to cause optic neuritis in both rat models and non-human primates. (*Id.* (citing F.X. Weilbach et al., *T-Cell Receptor V Beta-Element Expression in Peripheral Nerves of Lewis Rats Suffering from Experimental Autoimmune Neuritis,* 79 J. NEUROIMMUNOL. 69 (1997) (Ex. 52); Jeffrey Bajramovic et

al., *Oligodendrocyte-Specific Protein Is Encephalitogenic in Rhesus Macaques and Induces Specific Demyelination of the Optic Nerve,* 38 EUR. J. IMMUNOL. 1452 (2008) (Ex. 53)).) Alternatively, Dr. Akbari proposes another peptide to the major protein in the myelin sheath known as myelin basic protein in the influenza A vaccines. (Ex. 31, p. 7.) The amino acid sequence, FYKNLI, has high homology to myelin basic protein FFKNIV. (*Id.*) He explains that the only variations are one aromatic amino acid "f" for "y" and two aliphatic amino acids, leucine and isoleucine. (*Id.*) This, according to Dr. Akbari, is an undeniable example of molecular mimicry with influenza A strains that appear in the vaccine petitioner received.

Dr. Akbari explains that NAION is the most common form of ischemic optic neuropathy and the second most common form of optic neuropathy. (Ex. 31, p. 7.) He writes, "[i]t is presumed to be due to a transient disruption in the circulation of the optic nerve head leading to hypoperfusion and ischemia." (*Id.*) Several hypotheses have been proposed including generalized hypoperfusion, nocturnal hypotension, local autoregulation failure, vasospasm, venous inflammation, vasculitis and thrombosis. (*Id*. (citing Shauna Berry et al., *Nonarteritic Anterior Ischemic Optic Neuropathy: Cause, Effect, and Management*, 9 EYE & BRAIN 23 (2017) (Ex. 56)).) Although rare, Dr. Akbari opines that vasculitis has been reported as an adverse event following influenza vaccination. (*Id.*) Among 45 published reports, Watanabe identified 65 patients who developed vasculitis after influenza vaccination. (*Id.* (citing Toru Watanabe, *Vasculitis Following Influenza Vaccination: A Review of Literature*, 13 CURR. RHEUMATOL. REV. 188 (2017) (Ex. 57)).) Hadden et al. also reported several case reports with vasculitic neuropathy after influenza vaccination. (*Id.* (citing Robert Hadden et al., *Vasculitic Peripheral Neuropathy: Case Definition and Guidelines for Collection, Analysis, and Presentation of Immunization Safety Data*, 35 VACCINE 1567 (2017) (Ex. 58)).) Still other investigators also reported cases associating flu vaccination with optic neuropathy. (*Id.* (citing Emily Li & Adeniyi Fisayo, *Bilateral Reversible Optic Neuropathy After Influenza Vaccination*, 39 J. NEURO-OPHTHALMOL. 496 (2019) (Ex. 59); Kawasaki et al., *supra*, at Ex. 27 (also filed as Ex. 60)).)

Dr. Akbari further opines that cytokines may also play a role in inducing vasculitis. (Ex. 31, p. 8.) He observes that Song et al. published a meta-analysis to investigate possible associations between IL-1α, IL-1β, and IL-1 receptor antagonist (IL1RN) polymorphisms and vasculitis. (*Id.* (citing Song et al., *Associations Between Interleukin-1 Polymorphisms and Susceptibility to Vasculitis: A Meta-Analysis*, 75 Z. RHEUMATOL. 406 (2016) (Ex. 67)).) According to Dr. Akbari, the results strongly suggest that IL-1 polymorphism is associated with susceptibility to vasculitis. (*Id.*) Besides the IL-1 cytokine family, Dr. Akbari identifies other pro-inflammatory cytokines such as IL-6 which were associated with a strong ability to polarize immune cells to produce IL-17 and induce vasculitis and optic neuropathy. (*Id.* (citing Hajime Yoshifjui, *Pathophysiology of Large Vessel Vasculitis and Utility of Interleukin-6 Inhibition Therapy,* 29 MODERN RHEUMATOL. 287 (2019) (Ex. 68)).) Since these cytokines are "potent stimulators of adaptive responses," Dr. Akbari concludes that the inflammasome is likely a primary target causing vascular inflammation. (*Id.* (citing G.A. Ramirez et al.,

Intravascular Immunity as a Key to Systemic Vasculitis: A Work in Progress, Gaining Momentum, 175 CLIN. EXP. IMMUNOL. 150 (2014) (Ex. 69)).)

Still further, Dr. Akbari proposes a mechanism involving T cell dysfunction. (Ex. 31, pp. 8-9.) He opines that the influenza vaccine has been shown to stimulate regulatory T cells and T effector cells in normal individuals post-vaccination. (*Id.* at 9.) A balance in the levels of regulatory T cells and T effector cells maintains the homeostatic and disease-free state. (*Id.*) A shift in the balance towards T regulatory cells causes a decrease in anti-cancer immunity, resulting in cancer. (*Id.*) In contrast, a shift in the balance towards T effector cells causes a decrease in T regulatory cell levels and T effector cells hyperactivation—leading to autoimmune disorders, such as optic neuropathy. (*Id.*) In petitioner's case, Dr. Akbari proposes pathogenic T effector cells caused injury directly to the nerve or, alternatively, caused inflammation in the vascular system that resulted in optic nerve injury—simply due to T regulatory cells. (*Id.* (citing Huabin Zheng et al., *Increased Th17 Cells and IL-17 in Rats with Traumatic Optic Neuropathy*, 10 MOL. MED. REP. 1954 (2014) (Ex. 48); Shin-Min Wang et al., *The Regulatory T Cells in Antiinfluenza Antibody Response Post Influenza Vaccination*, 8 HUM. VACCIN. IMMUNOTHER. 1243 (2012) (Ex. 71); Thi Hong Khanh Vu et al., *CD4(+) T-Cell Responses Mediate Progressive Neurodegeneration in Experimental Ischemic Retinopathy,* 190 AM. J. PATHOL. 1723 (2020) (Ex. 72)).) Moreover, Dr. Akbari cites a cohort study of elderly patients who received the flu vaccine who demonstrated only a limited responsiveness to the vaccine, but a higher inflammatory status. (Ex. 31, p. 9 (citing I. Herrero-Fernandez et al., *Effect of Homeostatic T-Cell Proliferation in the Vaccine Responsiveness Against Influenza in Elderly People*, 16 IMMUNITY & AGEING 1 (2019) (Ex. 73)).) Dr. Akbari concludes that T regulatory cells post-flu vaccination "may trigger autoimmune diseases such as optic associated inflammation result[ing] in neuropathies in some individuals."

Lastly, Dr. Akbari opines that host susceptibility to the development of optic neuropathy is one of the most important factors in the development of the disease—and independent of the initiating pathologic cause. (Ex. 31, p. 9.) Specifically, he points to animal models, one using rodents and one using primates, of NAION that demonstrate the role of immune cells in creating inflammation leading to ocular damage. (*Id.* at 10-11 (citing Steven Bernstein et al., *Functional and Cellular Responses in a Novel Rodent Model of Anterior Ischemic Optic Neuropathy*, 44 INVEST. OPTHALMOL. VIS. SCI. 4153 (2003) (Ex. 78); Celia Chen et al., *A Primate Model of Nonarteritic Anterior Ischemic Optic Neuropathy*, 49 INVEST. OPHTHALMOL. VIS. SCI. 2985 (2008) (Ex. 79)).) Dr. Akbari acknowledges that these animal models have been criticized as not reflecting the true NAION because the experimental ischemic lesions are induced primarily in the intraretinal region of the central retinal artery circulation, rather than in the deeper posterior ciliary artery circulation. (*See id.*) While a model of the optic nerve injury that includes ON and NAION with conformity to the features of the human disease has yet to be created, Dr. Akbari stresses that "the cooperation between immune cells causing inflammation suggests it is likely that [the] genetic background of the host is a critical component to the pathogenesis of optic neuritis and NAION." (*Id.* at 11.)

b. Respondent's Expert, Michael Wilson, M.D., MAS

Dr. Wilson received his medical degree from the University of California, San Francisco School of Medicine. (Ex. C.) He completed his residency in neurology at the Harvard Neurology Residency Program at Massachusetts General Hospital and Brigham and Women's Hospital. (*Id.*) Dr. Wilson completed his clinical fellowship in neuro-infectious diseases at Massachusetts General Hospital. (*Id.*) Subsequently, he completed postdoctoral fellowships in neurovirology and metagenomics. (*Id.*) Dr. Wilson received his Master of Applied Science degree from the University of California, San Francisco. (*Id.*) He is a board-certified neurologist with subspecialty training in neuro-infectious diseases and neuroimmunology. (Ex. B, p. 1.) He serves as an associate professor of Neurology at UCSF in the Division of Neuroimmunology and Glial Biology and is a Principal Investigator of a lab "that has pioneered the development of metagenomic next-generation sequencing to diagnose neurologic infections in patients with meningitis, encephalitis and other neuroinflammatory conditions." (*Id.*) He has co-authored three *New England Journal of Medicine* publications and multiple publications in other top peer-reviewed journals. (*Id.*) In addition, his lab has developed comprehensive autoantibody and viral antibody discovery assays to search for antigenic targets and triggers of neuroinflammatory diseases, including multiple sclerosis and autoimmune encephalitis. (*Id.*) Dr. Wilson's research is funded by the National Institutes of Health, the National Multiple Sclerosis Society as well as several private foundations. (*Id.*)

Dr. Wilson agrees that "it is not clear that [petitioner's] clinical presentation was consistent with optic neuritis." (Ex. B, p. 4.) Dr. Wilson opines that "sequential NAION is a more likely diagnosis." (*Id*. at 5.) He summarizes, "[t]he petitioner's expert and I are in agreement that although optic neuritis cannot be completely excluded, the weight of the evidence favors the alternate diagnosis entertained by [petitioner's] treating physicians," NAION. (Ex. D, p. 1.)

Although Dr. Hedges opines that an immune complex vasculitis triggered by the influenza vaccine led to ischemic complications, Dr. Wilson stresses that petitioner's skin biopsy showed no clear evidence of vasculitis. (Ex. B, p. 4.) Moreover, Dr. Wilson observes that there is no record of a fluorescein angiogram to look for evidence of vasculitis in the retina, and systemic markers commonly associated with immune complex deposition, such as complement levels, are not available. (*Id.*)

Dr. Wilson also distinguishes petitioner's case from the case reports cited by Dr. Hedges. (Ex. B, p. 4.) Dr. Wilson stresses that the case reports of bilateral NAION cited by Dr. Hedges occurred sequentially after two separate influenza vaccinations whereas petitioner's bilateral optic nerve injury occurred after a single vaccination. (*Id.* (citing Manasseh et al., *supra*, at Ex. 29).) Both patients reported in Kawasaki et al. had eye pain which Dr. Wilson opines is more consistent with an optic neuritis than NAION. (*Id.* (citing Kawasaki et al., *supra*, at Ex. 27).) Moreover, the second case report by Kawasaki et al., had a coincident febrile systemic illness suggesting that in addition to the vaccination the patient also had an acute infection. (*Id.*) Lastly, the two cases

described in Kawasaki and the case reported by Ray and Dreizin had bilateral vision loss either occur simultaneously or within days of each other whereas petitioner's vision loss was truly sequential with his right eye becoming symptomatic only 2 months after the symptoms appeared in the left eye. (Ex. B, pp. 4-5.) According to Dr. Wilson "[i]t is this aspect of [petitioner's] case – the progressive and evolving illness over multiple months – that is importantly inconsistent with the short-lived, monophasic inflammatory reactions like optic neuritis and Guillain-Barré syndrome that are typically associated with vaccine complications." (Ex. D, p. 1.)

Dr. Wilson agrees that symptom onset 4 weeks post-vaccination is within the time window for post-vaccination syndromes. (Ex. B, p. 5.) However, Dr. Wilson contends that petitioner had a viral upper respiratory tract infection ("URI") even more proximate temporally to the onset of his vision symptoms. (*Id.*) He opines that there is no evidence suggesting that an influenza vaccination would be any more likely to trigger this process than a viral URI. (*Id.*) Moreover, he stresses that petitioner had a number of non-inflammatory risk factors for NAION. (Ex. D, p. 2.)

In response to Dr. Akbari, Dr. Wilson acknowledges that scientific literature might support the theory that rare immune responses to vaccination(s) can cause vascular inflammation. (Ex. E, p. 1.) However, he again stresses that petitioner's skin biopsy showed no clear evidence of vasculitis, nor are there any other results demonstrating an immune complex deposition. (*Id.*) Dr. Wilson suggests that petitioner's poor clinical response to a variety of immunosuppressive agents argues against his condition as having a significant inflammatory component as well. (*Id.* at 2.)

Dr. Akbari relies on literature demonstrating the association between non-vasculitic, demyelinating complications (e.g., optic neuritis) and influenza vaccination. In response, Dr. Wilson stresses that although petitioner's doctors reasonably speculated at various stages of his illness that optic neuritis was a diagnostic possibility, he continues to agree with petitioner's treating physicians that the evidence favors the alternate diagnosis of NAION. (Ex. E, p. 2.)

V. Discussion

a. Diagnosis

"The function of a special master is not to 'diagnose' vaccine-related injuries, but instead to determine 'based on the record as a whole and the totality of the case, whether it has been shown by a preponderance of the evidence that a vaccine caused the [petitioner]'s injury.'" *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1382 (Fed. Cir. 2009) (quoting *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 549 (Fed. Cir. 1994)). "Although the Vaccine Act does not require absolute precision, it does require the petitioner to establish an injury – the Act specifically creates a claim for compensation for 'vaccine-related injury or death.'" *Stillwell v. Sec'y of Health & Human Servs.*, 118 Fed. Cl. 47, 56 (2014) (quoting 42.U.S.C. § 300aa-11(c)). Accordingly, the Federal Circuit has concluded that it is "appropriate for the

special master to first determine what injury, if any, [is] supported by the evidence presented in the record before applying the *Althen* test to determine causation." *Lombardi v. Sec'y of Health & Human Servs*., 656 F.3d 1343, 1351-53 (Fed. Cir. 2011).

As noted during my prior Rule 5 conference, there was some uncertainty among petitioner's treating physicians as to petitioner's correct diagnosis – in particular optic neuritis versus NAION. (ECF No. 50.) In that regard, petitioner's motion for a ruling on the record includes some argumentation in his opening brief addressing optic neuritis. (ECF No. 65, pp. 29-30 n.16 (medical literature demonstrating a connection between vaccination and optic neuritis).) Additionally, petitioner suggests "should the Court find an expanded *Althen* analysis applied to the development of optic neuritis helpful to its consideration of petitioner's claim, petitioner can comply with such a request in his reply brief." (*Id.* at 29 n.15.) Such an expanded analysis is not warranted, however, because there is preponderant evidence on this record that petitioner suffered NAION. In fact, both parties have sections addressing diagnosis in their respective briefs in which they both explicitly confirm there is no dispute as to diagnosis – that diagnosis being NAION. (*Id.* at 27-29; ECF No. 66, p. 7.)

While petitioner's treating physicians were not definitive in their diagnosis, among the expert opinions offered in this case, both parties' experts agree that petitioner's correct diagnosis is NAION. (Ex. 30, p. 1; Ex. 31, p. 3; Ex. D, p. 1.) According to Dr. Hedges, NAION and optic neuritis have "overlapping clinical profiles." (Ex. 30, p. 1.) However, Dr. Hedges concludes on petitioner's behalf that petitioner suffers from an atypical presentation of NAION. (Ex. 24, p. 2.) Additionally, Dr. Wilson opines for respondent "petitioner's expert and I are in agreement that although optic neuritis cannot be completely excluded, the weight of the evidence favors the alternate diagnosis entered by [petitioner's] treating physicians," NAION. (Ex. D, p. 1.) Dr. Akbari noted that the possibility of optic neuritis was not ruled out, but likewise accepted the NAION diagnosis. (Ex. 31, pp. 1, 3.)

Importantly, the literature makes clear that optic neuritis and NAION are not the same condition and do not have the same etiology—NAION is ischemic / vascular rather than demyelinating. (Chen et al., *supra*, at Ex. 79, p. 1 (NAION "is an optic nerve (ON) stroke and a leading cause of sudden ON-related vision loss").) NAION is presumed to be due a transient disruption in the circulation of the optic nerve head leading to hypoperfusion and ischemia. (Berry et al., *supra*, at Ex. 56, p. 24.) The transient disruption is thought to be caused by generalized hypoperfusion, nocturnal hypotension, local autoregulation failure, vasospasm, venous occlusion, or thrombosis, though the exact cause remains unclear. (*Id.*) Still other patients are thought to be predisposed to NAION because of their small cup-to-disc ratio, or "crowded optic disk head." (*Id.*) When localized swelling occurs in a fixed space anterior to the rigid lamina cribosa, Barry et al. explain that the capillaries could become more easily compressed and secondary ischemia may result. (*Id.*) Systemic diseases, such as hypertension, diabetes, and hypercholesterolemia can cause decreased perfusion to the optic nerve head, secondary to microvascular compromise that puts individuals with these diseases at risk of NAION. (*Id.*) Dr. Wilson also draws this distinction between optic neuritis and

NAION in his report. (Ex. E, p. 2 (optic neuritis is "a non-vasculitic, demyelinating complication[]" unlike NAION).)

Prior cases in the Vaccine Program where petitioners have alleged vaccine-caused optic neuritis have addressed causation in terms of autoimmune demyelination. *Reinhardt v. Sec'y of Health & Human Servs.*, No. 17-1257V, 2021 WL 1851491, at *16 (Fed. Cl. Spec. Mstr. Apr. 2, 2021); *Althen v. Sec'y of Health & Human Servs.*, 58 Fed. Cl. 270, 285 (2003) (recognizing that optic neuritis represents a central demyelinating disease of the optic nerve and is not a "vasculitis" illness), *aff'd*, 418 F.3d 1274 (Fed. Cir. 2005). However, even setting aside a specific diagnosis, petitioner in this case exhibited no evidence of demyelination on MRI. (Ex. 3, pp. 52-55.) Moreover, given the record as a whole, the evidence favors the diagnosis of NAION entertained by petitioner's treating physicians and favored by both parties' experts, including most notably petitioner's own expert in neuro-ophthalmology. This points to a different underlying disease process. Thus, the fact that petitioner's NAION is preponderantly established does affect the resulting *Althen* analysis.[4]

b. *Althen* prong one

Under *Althen* prong one, petitioners must provide a "reputable medical theory," demonstrating that the vaccine received can cause the type of injury alleged. *Pafford*, 451 F.3d at 1355-56 (citations omitted). To satisfy this prong, petitioner's theory must be based on a "sound and reliable medical or scientific explanation." *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 548 (Fed. Cir. 1994). Such a theory must only be "legally probable, not medically or scientifically certain." *Id.* at 549. However, petitioners may satisfy the first *Althen* prong without resort to medical literature, epidemiological studies, demonstration of a specific mechanism, or a generally accepted medical theory. *Andreu v. Sec'y of Health & Human Servs.*, 569 F.3d 1367, 1378-79 (Fed. Cir. 2009) (citing *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1325-26 (Fed. Cir. 2006)).

Scientific evidence offered to establish *Althen* prong one is viewed "not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act's

[4] For example: In *Katz v. Secretary of Health & Human Services*, petitioner alleged that he suffered optic neuritis caused in fact by his hepatitis B vaccination. No. 04-714V, 2005 WL 6117659 (Fed. Cl. Spec. Mstr. Nov. 30, 2005). Petitioner's first expert proposed a diagnosis of optic neuritis, which was disputed by respondent's expert, who advocated an alternate diagnosis of ischemic optic neuropathy. *Id.* at *6. The special master found that petitioner more likely than not suffered from a non-demyelinating inflammatory optic neuritis. *Id.* at *18. Petitioner's expert was charged with explaining how petitioner's hepatitis B vaccination can cause and did cause her optic neuritis. *Id.* He offered the molecular mimicry theory to explain how the vaccine might have caused the production of antibodies, which then attacked healthy tissue. *Id.* However, the molecular mimicry theory proposed by Dr. Waisbren relied upon a similarity between a substance in the hep B vaccine and the myelin of the human nervous system. *Id.* The fatal flaw with this proposed mechanism was that petitioner exhibited no evidence of demyelination. *Id.* Without any evidence of demyelination, the special master found that "Dr. Waisbren's molecular mimicry proposal is of no use to explain how the hepatitis B vaccine may have caused petitioner's optic neuritis. Dr. Stivelman's diagnosis and Dr. Waisbren's theory of causation are mismatched." *Id.*

preponderant evidence standard." *Id.* at 1380. Accordingly, special masters must take care not to increase the burden placed on petitioners in offering a scientific theory linking vaccine to injury. *Contreras v. Sec'y of Health & Human Servs.*, 121 Fed. Cl. 230, 245 (2015) ("Plausibility . . . in many cases may be enough to satisfy *Althen* prong one."). But this does not negate or reduce a petitioner's ultimate burden to establish his entitlement to damages by preponderant evidence. *W.C. v. Sec'y of Health & Human Servs.*, 704 F.3d 1352, 1356 (Fed. Cir. 2013) (citations omitted). Nonetheless, although petitioners cannot be *required* to show "epidemiologic studies, rechallenge, the presence of pathological markers or genetic disposition, or general acceptance in the scientific or medical communities to establish a logical sequence of cause and effect" (*Capizzano*, 440 F.3d at 1325), the special master may consider and evaluate such evidence when filed. *Andreu*, 569 F.3d at 1379 (special masters may consider medical literature and epidemiological evidence, when it is submitted, in "reaching an informed judgment as to whether a particular vaccine likely caused a particular injury").

Petitioner's theory derives primarily from Dr. Akbari while Dr. Hedges principally relied on case reports. (Ex. 31, pp. 6-10; Ex. 24, p. 2.) Dr. Akbari proposes several theories ranging from molecular mimicry to vaccine-induced vasculitis to T-cell dysfunction. (Ex. 31, pp. 6-10.) However, as explained above, given that petitioner's NAION is preponderantly established, Dr. Akbari's extended discussion of demyelinating optic neuritis is irrelevant. On the whole, the literature filed in this case supports that NAION is likely due to a stroke-like mechanism affecting blood supply to the retina. (Chen et al., *supra*, at Ex. 79; Berry et al., *supra*, at Ex. 56; A.H. Ropper et al., eds. *Chapter 12: Disturbances of Vision*, *in* VICTOR'S PRINCIPLES OF NEUROLOGY (11th ed. 2019) (Ex. B, Tab 2); D. Vaughan et al., eds. *Chapter 14: Neuro-Ophthalmology*, *in* VAUGHAN & ASHBURY'S GENERAL OPHTHALMOLOGY (19th ed. 2004) (Ex. B, Tab 3); Nathan Kerr et al., *Non-Arteritic Anterior Ischaemic Optic Neuropathy: A Review and Update:* 16 J. CLIN. NEUROSCIENCE 994 (2009) (Ex. B, Tab 4).)

Both of petitioner's experts acknowledge that the pathophysiology of NAION is unknown. (Ex. 24, p. 3; Ex. 31, p. 8.) However, as the name suggests, both acknowledge that it results from ischemia. (Ex. 30, p. 1; Ex. 31, p. 8.) Dr. Akbari supports ischemia as underlying cause of NAION based on a number of publications, including experimental animal models. (Ex. 31 (citing Berry et al., *supra*, at Ex. 56; Khanh et al., *supra*, at Ex. 72; Chen et al., *supra*, at Ex. 79).) Notably, however, the animal models do not themselves include any studies examining vaccine-causation. (Khanh et al., *supra*, at Ex. 72; Bernstein et al., *supra*, at Ex. 78; Chen et al., *supra*, at Ex. 79; Hayreh, *supra*, at Ex. 80.) Moreover, gaps in petitioner's theory are further drawn out in Dr. Akbari's own concession that the animal models of NAION that he relies on "have been criticized as not reflecting true NAION." (Ex. 31, pp. 7, 10-11; *see also* Chen et al., *supra*, at Ex. 79; Hayreh, *supra*, at Ex. 80.) Additionally, in both Khanh et al. and Chen et al., the authors discuss how the retinal injury itself recruits inflammation to the eye in NAION. (Khanh, *supra*, at Ex. 72, p. 1732; Chen et al., *supra*, at Ex. 79, p. 7 ("the inflammation can cause increased tissue destruction, edema, and compression of adjacent vessels and axons, resulting in further loss of visual sensory function and decreasing the likelihood of significant visual recovery").) This

complicates any discussion of inflammation associated with NAION as being part of the etiology of the condition as opposed to a consequence of the condition.

Dr. Akbari's resulting theory otherwise turns largely on his broader discussion of post-vaccination vasculitis. (Ex. 31, pp. 7-8.) Importantly, however, not all vasculitides are the same. The vasculitides are a heterogenous group of disorders associated with organ dysfunction caused by inflammatory disease of blood vessels. (Hadden et al., *supra*, at Ex. 58, p. 1567.) The various clinical manifestations of different vasculitides depend on local immunologic environments, tissue vulnerabilities, and blood flow distributions. (*Id.*) Systemic vasculitis involves multiple organs and tissues, whereas in some patients, vasculitis is restricted to a single organ or tissue. (*Id.*) Thus, while Dr. Wilson conceded on respondent's behalf that "the scientific literature might support this general assertion about rare maladaptive immune responses to vaccinations causing vascular inflammation" (Ex. E, p. 1 (emphasis removed)), he was clear in opining that the fact that the flu vaccine might be capable of causing vasculitis in some contexts is not in itself evidence that it causes NAION.[5] (*Id.*) Rather, Dr. Wilson stresses that NAION is of unknown pathogenesis. (*Id.* at 1-2.) Examining the vasculitide literature relied upon by Dr. Akbari, he is not persuasive in linking vaccines to NAION.

Watanabe et al. (2017), sought reports of vasculitides following influenza vaccination. (Watanabe et al., *supra*, at Ex. 57.) Among 45 published reports the authors identified 65 patients. (*Id.* at 189.) As the study makes clear, not all forms of vasculitis have the same consequences. The authors divided the vasculitides of total cases into six major categories according to the predominant size of the vessel involved (large vessel, medium vessel, and small vessel vasculitis), single organ-involved vasculitis compared to systemic disease (rheumatoid vasculitis), and finally vasculitis associated with a probable etiology (HBV-associated vasculitis). (*Id.*) The small vessel vasculitides were further subdivided to ANCA-associated vasculitis, immune complex vasculitis, and unclassified. (*Id.*) The most frequently reported symptom was skin rash (37/57), followed by arthralgia or arthritis (31/57), fever (20/57) and malaise (15/57). (*Id.*) Unsurprisingly, the highest reported involved organ was skin (37/57), followed by joints (31/57), kidney (24/57), muscle (16/57), gastrointestinal tract (13/57), lung (10/57), peripheral nervous system (7/57), eye (8/57), central nervous system (7/57), and nose or mouth (3/57). (*Id.*) Dr. Akbari relies on this paper for the proposition that there were eight reports of ocular involvement. (Ex. 31, p. 7.) However, the eight cases he cites

[5] Special masters have likewise distinguished between different vasculitides in prior cases. *See Kelly v. Sec'y of Health & Human Servs.*, No. 17-1475V, *slip op.* (Fed. Cl. Spec. Mstr. Oct. 12, 2022) (distinguishing polymyalgia rheumatica and giant cell arteritis); *Suliman v. Sec'y of Health & Human Servs.*, No. 13-993V, 2018 WL 6803697 (Fed. Cl. Spec. Mstr. Nov. 27, 2018) (same); *see also Temes v. Sec'y of Health & Human Servs.*, No.16-1465V, 2020 WL 4198036 at *19-20 (Fed. Cl. Spec. Mstr. May 12, 2020) (distinguishing cryoglobulinemia and leukocytoclastic vasculitis); *Schultz v. Sec'y of Health & Human Servs.,* No. 16-539V, 2020 WL 1039161, at *7 (Fed. Cl. Spec. Mstr. Jan. 24, 2020) (criticizing Dr. Shoenfeld's opinion, in part, for conflating petitioner's stroke with vasculitis); *Guzman v. Sec'y of Health & Human Servs.*, No. 15-736V, 2019 WL 2723392, at *20 (Fed. Cl. Spec. Mstr. May 14, 2019) (distinguishing cutaneous vasculitis and chronic urticaria).

occurred in the context of ANCA-associated vasculitis, a broader systemic vasculitis.[6] (Watanabe et al., *supra*, at Ex. 57, p. 191.) That is not analogous to NAION. Only five cases overall involved single organ vasculitis and of those only one involved retinal arteritis. (*Id.*) None involved ischemic optic neuropathy, either arteritic or nonarteritic. (*See id.*) There was no indication that any particular vasculitis demonstrated a higher probability of vaccine-causation, though the most common type of vasculitis was small vessel vasculitis—somehow leading the authors to conclude that caution should be required for patients with small vessel vasculitis (in particular those with ANCA-associated or reactivated-IgAV vasculitis). (*Id.* at 193-94.) Among all the reported post-influenza vaccination vasculitides, Watanabe et al. concluded that the majority of studies did not find a causal association between vaccination and subsequent development of vasculitis. (*Id.* at 193.)

Hadden et al. (2017), reviewed twelve case reports proposing a possible association of vasculitis with previous immunization. (Hadden et al., *supra*, at Ex. 58, p. 1568.) Dr. Akbari cites this article presumably for the six cases reported post influenza vaccination. (*Id.*) However, this paper addresses the case definition and analysis for vasculitic peripheral neuropathy. (*Id.*) NAION is specifically identified as a CNS condition.[7] (Chen et al., *supra*, at Ex. 79, p. 2.) Vasculitic peripheral neuropathy typically manifests as an asymmetric neuropathy resulting from ischemic axonal injury. (Hadden et al., *supra*, at Ex. 58, p. 1567.) Unlike NAION, vasculitic neuropathies typically manifest with subacute stepwise progression or progressive worsening, although some patients exhibit more insidious chronic progression over many years. (*Id.* at 1568.) Even setting aside this distinction, Hadden et al. concluded that no causal relationship existed between immunization and systemic or nonsystemic (single-organ) vasculitic neuropathy has been established. (*Id.*)

Given the above, Dr. Akbari ultimately concludes only that "the scientific research supports the assertion that stimulation of the immune system following vaccinations is a *plausible* medical theory causally linking the influenza vaccination with the development of vasculitis and inflammation that resulted in symptoms in [petitioner] including optic neuropathy and vision loss." (Ex. 31, p. 10 (emphasis added).) Given that Dr. Akbari has only opined that petitioner's medical theory is "plausible," his opinion less helpful to petitioner in meeting his legal burden. *See*, *e.g.*, *Boatmon v. Sec'y of Health & Human Servs.*, 941 F.3d 1351, 1360 (Fed. Cir. 2019) (citing *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1322 (Fed. Cir. 2010)) (reaffirming that a "plausible" or "possible" causal theory does not satisfy a petitioner's burden).

[6] ANCA-associated vasculitides are a subgroup of small vessel vasculitis in which there are circulating antineutrophil cytoplasmic autoantibodies (ANCA). *ANCA-associated vasculitis,* DORLAND'S MEDICAL DICTIONARY ONLINE, https://www.dorlandsonline.com/dorland/definition?id=116898 (last accessed Nov. 9, 2022).

[7] NAION is an isolated infarct of the anterior optic nerve—the optic nerve "is a central nervous system (CNS) tract composed of retinal ganglion cell (RGC) axons that synapse in the lateral geniculate nuclei." (Chen et al., *supra*, at Ex. 79, p. 2.)

The remaining supporting evidence consists of case reports. Ray and Dreizin (1996) reported a 61-year-old woman who developed progressive visual loss in both eyes within three weeks following influenza vaccination. (Ray & Dreizin, *supra*, at Ex. 28.) Among the possible causes, the authors note the strong possibility of temporal arteritis, given the patient's age. (*Id.* at 183.) Temporal arteritis was ruled out, however, given the patient had no jaw claudication, headaches, fevers, or myalgias, or arthralgias. (*Id.*) Two separate sedimentation rates were normal and both temporal artery biopsies were negative. (*Id.*) Other ischemic causes such as small vessel disease associated with hypertensive disease were reportedly considered, however, the authors indicated that "these rarely occur in both eyes simultaneously, and the patient [here] was healthy." (*Id.* at 183-84.) A compressive mass or infiltrative tumor was excluded on MRI and by the normal histopathology of the optic nerve sheath. (*Id.* at 184.) Laboratory tests also ruled out meningeal carcinomatosis, sarcoid, Lyme disease, Leber's optic neuropathy, and systemic lupus. (*Id.*) A heavy metal screening revealed elevated mercury—and while mercury has been reportedly associated with peripheral neuropathies and cerebellar symptoms, the authors stress that it has not been causally associated with optic neuropathies. (*Id.*) The authors stress that optic neuropathy is a diagnosis of exclusion. (*Id.*) While Ray and Dreizin suggest it is possible their patient's abrupt onset of bilateral vision loss was caused by the influenza vaccine, the authors acknowledge several caveats. (*Id.*) First, optic neuropathy does not follow influenza vaccination as often as acute inflammatory demyelinating polyneuropathy (GBS). (*Id.*) While the patient's visual recovery coincided with restarting steroids—the authors question: "Was her recovery due just to time or was it from the combined use of prednisone, or from the prednisone alone?" (*Id.*) Lastly, the authors note that their patient underwent a left optic nerve sheath fenestration ("ONSF") at the time she restarted prednisone—"which too may have played a role in her recovery." (*Id.*)

Kawasaki et al. (1998), reported two cases of anterior ischemic optic neuropathy following influenza vaccination. (Kawasaki et al., *supra*, at Ex. 27.) The first case was a 47-year-old woman who complained of decreased vision in her right eye one week after her influenza vaccination—associated with transient eye pain. (*Id.* at 56.) Five days later she developed blurriness in the left eye. (*Id.*) The patient demonstrated moderately edematous optic discs with splinter hemorrhages and cotton-wool spots. (*Id.*) Her laboratory tests were largely normal. (*Id.*) She was treated with prednisone and subsequently developed segmental disc atrophy—the results of her examination remained unchanged at one year. (*Id.*) The second case involved a 51-year-old woman who became febrile with chills and myalgias one-day post vaccination. (*Id.*) These symptoms resolved over three weeks. (*Id.*) Four weeks later, she complained of ear pain, headache, and blurry vision—first in her right eye then in her left eye. (*Id.*) Both optic discs were edematous. (*Id.*) Despite IV methylprednisolone, her vision progressively worsened over several weeks. (*Id.*) Lab tests were all normal except for disc edema. (*Id.*) Her visual function was unchanged at two months, and bilateral optic disc atrophy had developed. (*Id.* at 57.) The authors proposed two possible mechanisms for the lack of visual recovery, either (1) an allergic cross-reaction to viral antigens stimulating optic nerve inflammation and demyelination severe enough to cause direct axonal injury or (2) immune-mediated vasculitis causing ischemic optic

neuropathy. (*Id.* at 58.) However, the authors expressly note that "[n]o pathologic examination of vaccination-associated optic neuritis currently exists to help differentiate these two mechanisms." (*Id.* at 58-59.)

Manasseh et al. (2014), reported a case of a 68-year-old man who developed bilateral NAION, with each episode occurring in close temporal proximity to influenza vaccination. (Manasseh et al., *supra*, at Ex. 29.) The patient reported a two-day history of reduced visual acuity ten days after receiving an influenza vaccine. (*Id.* at 267.) The patient was subsequently diagnosed with AION, which was later refined to NAION. (*Id.* at 268.) Over the next three months the patient's visual acuity in the left eye recovered with a persistent field defect. However, the following year, six days after receiving the influenza vaccine, he returned with a new-onset visual field defect in his right eye. (*Id.*) Ocular findings were again normal apart from swelling in the superior disc margin in the right eye, and laboratory studies excluded giant cell arteritis. (*Id.*) The patient was treated with a prednisone taper. (*Id.*) The authors observed that the patient was over 65, had a history of diabetes mellitus and was hypermetropic with small optic discs and taking tadalafil—"all of which are known or potential risk factors for NA-AION." (*Id.*) Moreover, the authors point out that the cumulative incidence of second-eye involvement in NA-AION is 18% at one year and 25% at three years. (*Id.*) Taken together, Manasseh et al. report "our case probably represents a chance occurrence, especially as there is some evidence that within-season influenza vaccination leads to a reduced incidence of stroke and other cardiovascular events." (*Id.*)

Li & Fisayo (2019) reported a case of bilateral optic neuritis occurring one week after influenza vaccination in a previously healthy six-year-old child. (Li & Fisayo, *supra*, at Ex. 59, p. 496.) Examination revealed severe optic disc swelling with vessel obscuration bilaterally and peripapillary hemorrhages on the left. (*Id.*) MRI of the brain, orbits, and spinal cord showed increased T2/FLAIR signal and abnormal enhancement in the retrobulbar optic nerves bilaterally, but no white matter lesions in the brain or spinal cord. (*Id.*) Six days after the last dose of IV steroids, the patient experienced decreased vision in the left eye. (*Id.*) The patient started oral prednisone, and two weeks later visual acuities returned to 20/20 with normal color vision in each eye. (*Id.*) There is no indication that this patient had NAION.

Generally, case reports offer circumstantial evidence of vaccine causation and therefore should not be summarily rejected. Case reports "'do not[, however,] purport to establish causation definitively, and this deficiency does indeed reduce their evidentiary value'. . . [but] 'the fact that case reports can by their nature only present indicia of causation does not deprive them of all evidentiary weight.'" *Paluck v. Sec'y of Health & Human Servs.*, 104 Fed. Cl. 457, 475 (2012) (quoting *Campbell v. Sec'y of Health & Human Servs.*, 97 Fed. Cl. 650, 668 (2011), *aff'd*, 786 F.3d 1373 (Fed. Cir. 2015)). Case reports often present a detailed report of symptoms, signs, diagnosis, treatment, and follow-up care. Oftentimes petitioners in the Program will highlight the usefulness of case reports in cases of novel, unusual or rare diseases. *See Patton v. Sec'y of Health & Human Servs.*, 157 Fed. Cl. 159, 166-67 (2021). *But see Crutchfield v. Sec'y of Health & Human Servs.*, No. 09-39V, 2014 WL 1665227, at *19 (Fed. Cl. Spec. Mstr.

Apr. 7, 2014) ("single case reports of Disease X occurring after Factor Y . . . do not offer strong evidence that the *temporal* relationship is a *causal* one—the temporal relationship could be pure random chance"), *aff'd*, 125 Fed. Cl. 251 (2014).

Here, I am not persuaded by respondent's contention that eye pain suggestive of optic neuritis is dispositive where Kawasaki et al. are clear in concluding that the diagnosis is NAION. Both patients suffered eye pain which Dr. Wilson opines is more consistent with an optic neuritis than NAION. (Ex. B, p. 4 (citing Kawasaki et al., *supra*, at Ex. 27).) Indeed, some researchers consider eye pain to be an atypical feature for NAION. (Berry et al., *supra*, at Ex. 56, p. 24.) Moreover, Kawasaki et al. acknowledge that optic neuritis can present with bilateral vision loss and optic disc edema may or may not present acutely. (Kawasaki et al., *supra*, at Ex. 27, p. 56.) The presentation of both patients in Kawasaki's case report would have been seemingly atypical for both AION and optic neuritis. (*See id.*) Yet, Kawasaki et al. concluded that in their two patients, the pattern of visual field loss, segmental disc changes, and failure of visual recovery is more consistent with AION than with a demyelinating optic neuritis. (*Id.* at 59.) However, I am persuaded by the fact that the case reports filed in this case describe acute onset—whereas petitioner had sequential onset approximately two months after the symptoms appeared in the left eye. (Kawasaki et al., *supra*, at Ex. 27; Ray & Dreizin, *supra*, at Ex. 28.) In his second report, Dr. Wilson notes this is in contrast to acute monophasic conditions that are typically associated with vaccines. (Ex. D, p. 1.) The issue here is that a fluctuating condition in one eye might be explained by the resulting nerve damage from the initial inflammatory event. But to have a new onset occurring in a separate eye at a separate time speaks to some kind of chronicity in the underlying cause that is not necessarily consistent with vaccine causation.[8]

At first blush, the case report from Manasseh suggests the possibility for a challenge-rechallenge event.[9] Respondent argues this is immaterial because there is no evidence petitioner experienced a recurrence of NAION after a second dose of flu vaccine. (ECF No. 66, p. 11 n.4.) However, I find that this is a factor that increases the evidentiary value of that case report. The Institute of Medicine (IOM) "has stated that rechallenge is proof of causation . . . The IOM has also stated that where causation is

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[8] Relatedly, Dr. Akbari observes that petitioner experienced optic disc swelling in his *right eye* approximately one month after the steroid taper. (Ex. 31, p. 4 (citing Ex. 8, pp. 6-10).) Though, on the other hand, Dr. Wilson stresses that petitioner only ever had an incomplete response to steroid treatment. (Ex. B, p. 4.) When patients respond well to steroids, it is support of an inflammatory etiology (e.g., optic neuritis). (*Id.*)

[9] Within the context of the Vaccine Program, the Federal Circuit has described:

> A rechallenge event occurs when a patient who had an adverse reaction to a vaccine suffers worsened symptoms after an additional injection of the vaccine. The chief special master stated that this evidence of rechallenge constituted 'such strong proof of causality that it is unnecessary to determine the mechanism of cause—it is understood to be occurring.'

Capizzano, 440 F.3d at 1322 (internal citation omitted).

proven, biologic plausibility is a given." *Capizzano v. Sec'y of Health & Human Servs.*, 2004 WL 1399178, *2 (Fed. Cl. Spec. Mstr. 2004) (citing Christopher P. Howson et al., Institute of Medicine, *Adverse Effects of Pertussis and Rubella* Vaccines, 48, 53 (1991); Kathleen R. Stratton et al., Institute of Medicine, *Adverse Events Associated with Childhood Vaccines: Evidence Bearing on Causality,* 21 (1994)). It was not disputed that the petitioner in *Capizzano* did not suffer a challenge-rechallenge event. *Capizzano v. Sec'y of Health & Human Servs.*, 2006 WL 3419789, at *12 (Fed. Cl. Spec. Mstr. 2006). However, what I find most critical in this case report is the authors' overall conclusion that the patient's development of sequential bilateral NAION was a chance occurrence—noting the patient's risk factors for developing NAION independent of the vaccine administered. (Manasseh et al., *supra*, at Ex. 29, p. 268.)

On balance, the case reports provide some support for petitioner's claim, but not enough without more given that the causes of NAION are unknown. *See*, *e.g.*, *W.C. v. Sec'y of Health & Human Servs.*, No. 07-456V, 2011 WL 4537887, at *13 (Fed. Cl. Spec. Mstr. Feb. 22, 2011) ("case reports are generally weak evidence of causation because case reports cannot distinguish a temporal relationship from a causal relationship"), *mot. for review den'd*, 100 Fed. Cl. 440 (2011), *aff'd*, 704 F.3d 1352 (Fed. Cir. 2013); *Caves v. Sec'y of Health & Human Servs.*, No. 07-443V, 2010 WL 5557542, at *14 (Fed. Cl. Spec. Mstr. Nov. 29, 2010) ("case reports do[] not help [petitioners] meet [their] burden of demonstrating a persuasive and reliable theory causally connecting" vaccine to injury), *mot. for review den'd*, 100 Fed. Cl. 119 (2011), *aff'd*, 463 Fed. App'x 932 (Fed. Cir. 2012); *Ryman v. Sec'y of Health & Human Servs.*, 65 Fed. Cl. 35, 39 (2005) ("case reports are the least reliable type of evidence for establishing vaccine injury causation"); *Pearson v. Sec'y of Health & Human Servs.*, No. 17-489V, 2019 WL 1150044, at *11 (Fed. Cl. Spec. Mstr. Feb. 7, 2019) (noting that "probative weight given to [case reports] in Program cases is limited"); *Knorr v. Sec'y of Health & Human Servs.*, No. 15-1169V, 2018 WL 6991548, at *30 (Fed. Cl. Spec. Mstr. Dec. 7, 2018) ("substantial authority also notes that case reports are not robust evidence favoring causation (even under the Program's comparatively lenient preponderance evidentiary standard)").

Taking all of this together, petitioner's claim that the flu vaccine can cause NAION is not preponderantly supported. Dr. Akbari offered molecular mimicry to explain how the vaccine might have caused the production of antibodies, which subsequently attacked healthy tissue. However, the molecular mimicry theory proposed by Dr. Akbari relies upon a similarity between a substance in the flu vaccine and the myelin of the human nervous system. The fatal flaw with this proposed mechanism is that NAION is ischemic / vascular rather than demyelinating. Without any evidence of demyelination, Dr. Akbari's molecular mimicry proposal is of no use to explain how the flu vaccine may have caused petitioner's NAION. Dr. Akbari's further reliance on a broader discussion of vasculitis is likewise unpersuasive. Nor do the case reports cited by Drs. Akbari and Hedges provide preponderant support. Thus, for all these reasons, petitioner has not met his burden under *Althen* prong one.

c. *Althen* prong two

The second *Althen* prong requires proof of a logical sequence of cause and effect, usually supported by facts derived from a petitioner's medical records. *Althen*, 418 F.3d at 1278; *Andreu*, 569 F.3d at 1375-77; *Capizzano*, 440 F.3d at 1326; *Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992). In establishing that a vaccine "did cause" the injury, the opinions and views of the injured party's treating physicians are entitled to some weight. *Andreu*, 569 F.3d at 1367; *Capizzano*, 440 F.3d at 1326 ("medical records and medical opinion testimony are favored in vaccine cases, as treating physicians are likely to be in the best position to determine whether a 'logical sequence of cause and effect show[s] that the vaccination was the reason for the injury'") (quoting *Althen*, 418 F.3d at 1280). Medical records are generally viewed as particularly trustworthy evidence, since they are created contemporaneously with the treatment of the patient. *Cucuras v. Sec'y of Health & Human Servs.*, 993 F.2d 1525, 1528 (Fed. Cir. 1993).

However, medical records and/or statements of a treating physician's opinion do not *per se* bind the special master to adopt the conclusions of such an individual, even if they must be considered and carefully evaluated. *See* § 13(b)(1) (providing that "[a]ny such diagnosis, conclusion, judgment, test result, report, or summary shall not be binding on the special master or court"); *Snyder v. Sec'y of Health & Human Servs.*, 88 Fed. Cl. 706, 746 n.67 (2009) ("there is nothing ... that mandates that the testimony of a treating physician is sacrosanct—that it must be accepted in its entirety and cannot be rebutted"). As with expert testimony offered to establish a theory of causation, the opinions or diagnoses of treating physicians are only as trustworthy as the reasonableness of their suppositions or bases. The views of treating physicians should also be weighed against other, contrary evidence also present in the record—including conflicting opinions among such individuals. *Hibbard v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 742, 749 (2011) (not arbitrary or capricious for special master to weigh competing treating physicians' conclusions against each other), *aff'd*, 698 F.3d 1355 (Fed. Cir. 2012); *Caves v. Sec'y of Health & Human Servs.*, 100 Fed. Cl. 119, 136 (2011), *aff'd*, 463 Fed. App'x 932 (Fed. Cir. 2012); *Veryzer v. Sec'y of Health & Human Servs.*, No. 06-522V, 2011 WL 1935813, at *17 (Fed. Cl. Spec. Mstr. Apr. 29, 2011), *mot. for review den'd*, 100 Fed. Cl. 344, 356 (2011), *aff'd without opinion*, 475 Fed. App'x 765 (Fed. Cir. 2012).

Petitioner stresses that his treating physicians documented the onset of his vision loss "in the context of his recent flu vaccination repeatedly." (ECF No. 65, p. 37 (citing Ex. 8, p. 2 (Dr. Potter 12/9/2016); Ex. 4, p. 43 (Dr. Sharma 12/9/2016); Ex. 8, p. 5 (Dr. Samy 1/5/2017); Ex. 8, p. 10 (Dr. Samy 1/27/2017); Ex. 8, p. 15 (Dr. Samy 2/2/2017); Ex. 8, p. 21 (Dr. Samy 2/17/2017); Ex. 8, p. 38 (Dr. Samy 5/19/2017); Ex. 21, p. 3 (Dr. Samy 11/12/2018)).) However, the context of those records reveals that his treaters considered vaccine-causation within the context of a differential diagnosis that concurrently considered the possibility of infectious and autoimmune etiologies. In each of Dr. Samy's reports he additionally notes "suspected post-vaccination vs post-infectious vs autoimmune optic neuritis (MS-spectrum)." (Ex. 8, pp. 2, 5, 10, 15, 21,

38.) The notation from Dr. Sharma in the emergency department similarly reflects "[a]s per ophthalmology he has most likely post-vaccination optic neuritis . . . vs post-infectious optic neuritis . . . vs autoimmune optic neuritis." (Ex. 4, p. 43.) In petitioner's final visit with Dr. Samy on November 11, 2018, he noted that petitioner "developed optic neuropathy [in] early 2017 which was post vaccination *but in a pattern suggestive of possible ischemia* in disc without cup followed by a few months later with the other eye." (Ex. 21, p. 3 (emphasis added).) Considering Dr. Samy's records as a whole, his statements of mere suspicion fall short of an opinion supporting a vaccine-causation of petitioner's condition. *See Cedillo v. Sec'y of Health & Human Servs.*, 617 F.3d 1328, 1348 (Fed. Cir. 2010) (special master did not err in affording little weight to the opinions of petitioner's treating physicians where "none of the treating physicians concluded that the MMR vaccine caused [petitioner's] autism"); *Moberly*, 592 F.3d at 1324-25 (finding no treating physician evidence to support the claim of causation where the "medical records regarding the temporal proximity of the [vaccination] to the seizures were all speculative"); *Stapleford v. Sec'y of Health & Human Servs.*, No. 03-234V, 2009 WL 1456441, at *17 n.24 (Fed. Cl. Spec. Mstr. May 1, 2009) (referencing medical record "is quite different from an indication that such physician has reached a *conclusion* concerning a causal relationship") (emphasis in original), *aff'd*, 89 Fed. Cl. 456 (Fed. Cl. 2009). Moreover, "[a] treating physician's recognition of a temporal relationship does not advance the analysis of causation." *Isaac v. Sec'y of Health & Human Servs.*, No. 08-601V, 2012 WL 3609993, at *26 (Fed. Cl. Spec. Mstr. July 30, 2012); *see also Devonshire v. Sec'y of Health & Human Servs.*, No. 99-031V, 2006 WL 2970418, at *19 (Fed. Cl. Spec. Mstr. Sept. 28, 2006) (medical expert's "*post hoc ergo prompter hoc* reasoning . . . has been consistently rejected by the Court and is 'regarded as neither good logic nor good law'") (quoting *Fricano v. U.S.*, 22 Cl. Ct. 796, 800 (1991) (emphasis in original)).

However, I am also not persuaded that respondent has presented petitioner's prior infection as a significant consideration. Respondent stresses that petitioner had an upper respiratory infection roughly two weeks prior to the onset of his symptoms, "which under his experts' causation theory would be just as likely to have caused petitioner's NAION." (ECF No. 66, p. 1.) In his second report, however, Dr. Wilson agrees the relationship between infection and NAION is unclear. (Ex. D, p. 1.) Nor does the medical literature filed in this case bear out any suspected infectious etiology. Indeed, upon initial presentation, petitioner's treating physicians felt a post-infectious injury was less likely given his negative labs. (Ex. 8, p. 2.)

However, Dr. Wilson also discussed other factors relevant to *Althen* prong two. First, and most notably, petitioner had other non-inflammatory risk factors for NAION including hypertension, smoking, age, and sleep apnea. (Ex. 5, pp. 1-2, 13; Ex. 7, p. 2; Ex. 2, p. 5.) As Berry et al. explained:

> Systemic diseases that may cause decreased perfusion to the optic nerve head secondary to microvascular compromise might increase the patient's risk of NAION. These include hypertension, diabetes, and hypercholesterolemia. Other risk factors noted in the literature are

> nocturnal hypotension, smoking, obstructive sleep apnea, anemia, hypercoagulable states, disc drusen, ocular and nonocular surgery, and migraines.

(Berry et al., *supra*, at Ex. 56, p. 2; *see also* Kerr et al., *supra*, at Ex. B, Tab 4, pp. 2-3; Vaughan et al., *supra*, at Ex. B, Tab 3, pp. 25-26.) Dr. Hedges acknowledges that petitioner had risk factors for NAION but attempts to minimize this fact by suggesting "these are associations, not direct causative factors." (Ex. 24, p. 2.) However, this is not persuasive given that Dr. Hedges nonetheless further opines that the risk factors were contributory in petitioner's own case. Specifically, he opined that "[t]hese risk factors combined with a physiologic response to vaccination" ultimately caused petitioner's optic nerve injury. (*Id*.) Dr. Wilson also stresses that petitioner's skin biopsy showed no clear evidence of vasculitis. (Ex. B, p. 4.) Moreover, Dr. Wilson observes that there is no record of a fluorescein angiogram to look for evidence of vasculitis in the retina, and systemic markers commonly associated with immune complex deposition, such as complement levels, are not available. (*Id.*)

Overall, petitioner has not preponderantly proven that his flu vaccination did cause his NAION. Though some of his treating physicians considered and reported a temporal association, none concluded that his vision loss was caused by his flu vaccination. Moreover, petitioner has not preponderantly demonstrated a logical sequence of cause and effect implicating his vaccination as a cause of his injury. Thus, petitioner has not met his burden under *Althen* prong two.

d. *Althen* prong three

The third *Althen* prong requires establishing a "proximate temporal relationship" between the vaccination and the injury alleged. *Althen*, 418 F.3d at 1281. That term has been equated to the phrase "medically-acceptable temporal relationship." *Id.* A petitioner must offer "preponderant proof that the onset of symptoms occurred within a timeframe which, given the medical understanding of the disorder's etiology, it is medically acceptable to infer causation." *Bazan v. Sec'y of Health & Human Servs.*, 539 F.3d 1347, 1352 (Fed. Cir. 2008). The explanation for what is a medically acceptable timeframe must also coincide with the theory of how the relevant vaccine can cause an injury (*Althen* prong one's requirement). *Id.* at 1352; *Shapiro v. Sec'y of Health & Human Servs.*, 101 Fed. Cl. 532, 542 (2011), *recons. den'd after remand*, 105 Fed. Cl. 353 (2012), *aff'd mem.*, 503 Fed. App'x 952 (Fed. Cir. 2013); *Koehn v. Sec'y of Health & Human Servs.*, No. 11-355V, 2013 WL 3214877 (Fed. Cl. Spec. Mstr. May 30, 2013), *mot. for review den'd*, (Fed. Cl. Dec. 3, 2013), *aff'd*, 773 F.3d 1239 (Fed. Cir. 2014).

Here, because petitioner has failed to meet his preponderant burden pursuant to *Althen* prongs one and two, he cannot prevail. In the interest of completeness, however, I note briefly that respondent's expert, Dr. Wilson, agrees with the contention that "symptom onset approximately 4 weeks after vaccination is within the time window for post-vaccination syndromes." (Ex. B, p. 5.) He specifically stated that the timing of petitioner's symptoms "could be consistent with a vaccine-triggered complication." (*Id*.)

Accordingly, had petitioner proven his case with respect to the first two *Althen* prongs, it is likely he would have also prevailed with regard to *Althen* prong three.

VI. Conclusion

Petitioner has my sympathy for the injury he endured. Considering the record as a whole under the standards applicable in this Program, however, petitioner has not preponderantly established either that his October 28, 2016, flu vaccination caused his condition. Accordingly, petitioner is not entitled to compensation. Therefore, this case is dismissed.[10]

IT IS SO ORDERED.

s/Daniel T. Horner
Daniel T. Horner
Special Master

[10] In the absence of a timely-filed motion for review of this Decision, the Clerk of the Court shall enter judgment accordingly.